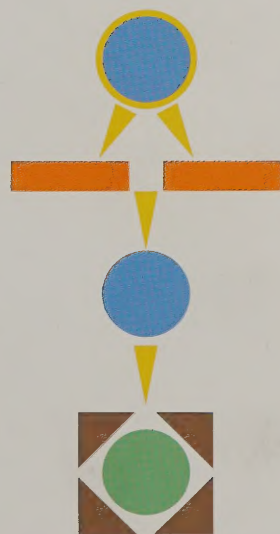


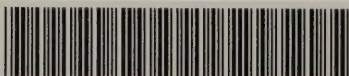
**STRATEGY FOR RESEARCH AND  
DEVELOPMENT RELATING TO THE  
HUMAN HEALTH ASPECTS OF  
TRANSMISSIBLE SPONGIFORM  
ENCEPHALOPATHIES**



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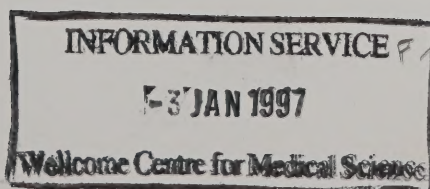
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# STRATEGY FOR RESEARCH AND DEVELOPMENT RELATING TO THE HUMAN HEALTH ASPECTS OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

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## **PREFACE**

This strategy for research into the human aspects of transmissible spongiform encephalopathies results from the remit given to the Director of Research and Development of the Department of Health by the Secretary of State. The Director was charged with developing a comprehensive programme of R&D which included the other major funders in this area. Accordingly, priority areas have been highlighted as requiring further research, in order to elucidate currently unanswered questions that may impact on human health and its protection.

In essence, the report lays out a statement of R&D requirements and it is against this statement that future R&D will be commissioned. All the major funders have already given new priority to research in this area and have begun to incorporate the priority areas into their individual research strategies. In the UK there has been a long history of funding TSE research and in the last 5 years alone a total of £76 million has been invested in this area.

I have drawn on a wide range of advice – from SEAC, from members of other advisory groups and from individual experts. I am particularly indebted to Professor Les Borysiewicz from the University of Wales, College of Medicine who chairs the Research Advisory Group.

This field is changing with dramatic rapidity. Resolution of the important problems posed by TSEs requires a contribution from a number of scientific disciplines. Basic understanding of the nature of the infective agent will lead to new approaches to diagnosis and management. It is encouraging that a number of our most distinguished scientists are putting their skills to this important task already. The major resources being invested by the funding bodies in the areas outlined in this strategy will build on this. The pace of change inevitably means that the strategy will require regular reassessment as new knowledge accumulates.

The identification of this new variant of CJD and its possible link with BSE poses an enormous challenge to the scientific community. The work carried out in pursuit of this strategy will make a major and urgently needed contribution to the protection of public health.

Professor John Swales

DIRECTOR OF RESEARCH AND DEVELOPMENT  
DEPARTMENT OF HEALTH

## **ERRATUM**

**Page i, paragraph 2, line 5; “...£50 million has been invested in this area”**



## EXECUTIVE SUMMARY

The Director of Research and Development for the Department of Health was remitted by the Secretary of State to mount a directed programme of R&D relating to the human health aspects of transmissible spongiform encephalopathies (TSEs). As a result, this strategy, outlining the priority issues that need research attention has been developed, through wide consultation with the main funders in the field and with the relevant scientific community.

The strategy identifies the main funders in the field are the Ministry of Agriculture, Fisheries and Food (MAFF), Medical Research Council (MRC), Biotechnology and Biological Sciences Research Council (BBSRC) and the Health Departments (HDs). Other funders include the Wellcome Trust and the Health and Safety Executive (HSE). The importance of European and international collaboration is emphasized.

The aim of this strategy is to lay out important issues in this field, where greater research understanding is needed to inform appropriate policy and remedial action. We need to know precisely what agent causes Creutzfeldt-Jacob disease (CJD) and how it develops in humans. The strategy recognizes the wide range of fundamental and applied questions that need answering if knowledge is to be usefully advanced in this area. It identifies a priority need for R&D in the following areas:-

- the nature of the biological agent causing this group of diseases and whether there is one or several strains of the new variant CJD;
- the determination of the relationship between BSE and CJD, and whether BSE can pass to humans as new variant CJD; how these diseases are transmitted both *within* and *between* species; further exploration of maternal transmission and transmission by horizontal routes, including oral and other mechanisms;
- development of efficient diagnostic techniques vital to early detection of the disease, to tracking how the disease progresses within the body; to checking the effectiveness of promising treatments and to epidemiological surveillance;
- issues of public health protection including the continued investigation of food and environmental safety, worker protection, the safety of medical procedures and the search for effective methods of decontamination;
- development of therapeutics for CJD;
- surveillance and epidemiology, to check that cases have not been overlooked by intensive examination of young and elderly populations; and predictive modelling of CJD in the population based on the BSE epidemic.

The strategy notes that the research endeavour is likely to be long term and raises issues relating to workforce capacity and infrastructural requirements.

The strategy describes which funding body is responsible for taking forward which parts of the research requirement, and the current and future plans of the main funders are documented. The joint DH/MRC TSEs Research Advisory Group is in place and the DH TSE R&D Funders Coordination Group will ensure the strategy moves forward in a pro-active and coordinated way.

Although the strategy is now being published for the first time, much of the work described is underway, supported by the funding bodies. It is also important to emphasize that this strategy is not a static one; it will be kept under continuous review as scientific understanding develops.

### **Reason for a new strategy**

1. In March 1996 a new variant of Creutzfeldt-Jacob disease (nvCJD) was described; the scientific view was that, the most likely explanation was that the cases were linked to exposure to bovine spongiform encephalopathy (BSE) before the introduction of the Specified Bovine Offal (SBO) ban in 1989. This new information relating to a potential risk to public health from BSE, focused attention on the need for a renewed strategy for research into transmissible spongiform encephalopathies (TSEs).
2. Research on TSEs has a long history, with an early focus on scrapie in sheep, and seminal work on the spongiform encephalopathies (SEs) in man covering kuru, and epidemiological work on familial, iatrogenic and sporadic CJD. Detailed work on BSE began immediately after the disease was first identified in 1986. Initially, it focused on characterising the disease and determining its cause. The main aims quickly changed to address issues of basic biology, transmissibility, and diagnosis, so that measures could be taken to eradicate the disease in animals and protect public health.
3. In 1989 the Tyrell Committee and the subsequent Spongiform Encephalopathies Advisory Committee (SEAC) were commissioned to advise both the Ministry of Agriculture, Fisheries and Food (MAFF) and the Department of Health (DH) on appropriate research. The SEAC Report "Transmissible Spongiform Encephalopathies - A Summary of Present Knowledge and Research" published in September 1994 summarises knowledge in this field at that date and reflects the considerable research programme, largely focusing on BSE and scrapie, already in train, funded by the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC) and MAFF. Since that date, research has continued and has been fundamental to clarifying the nature of the problem.
4. The Secretary of State for Health has given the DH Director of Research and Development a remit to mount a directed programme of research and development (R&D) in this area, involving other funders. This paper lays out the strategy against which the directed programme of the relevant funders will need to be commissioned.

### **The importance of R&D to the protection of human health**

5. The identification of the nvCJD and its possible link to BSE, represents a potential risk to public health, particularly in relation to food safety. Public concern continues to run at a high level in the UK and in Europe. While all public health precautionary measures that are seen to be necessary have been put in place, the lack of knowledge about the basic nature of the transmissible agent and the causal mechanisms of disease, mean that preventive measures to protect public health, may currently be over cautious or wrongly targeted. The effects for agriculture, pharmaceutical, and related commercial concerns are considerable. There is pressure on the UK from Europe, and from the World Health Organization (WHO), not only to take prudent public health measures, but also to mount the R&D that continues to be necessary to resolve some of the major uncertainties in the scientific knowledge base.

## **Introduction to the R&D strategy**

6. The aim of this paper is to lay out the important issues related to spongiform encephalopathies where greater understanding is needed to inform the development of policy and appropriate remedial action. The focus of the paper is on the human health aspects, but, in many cases it is not possible to disassociate these from issues of animal health. Many of the key questions to be answered, require the testing of shared hypotheses, often using the same scientific methods supported by shared infrastructure.
7. The paper lays out a national strategy, with the health of the nation as a guiding objective and does not reflect the perspective of any individual R&D funder or field of research.
8. The considerable body of knowledge about spongiform encephalopathies in animals, notably BSE and scrapie, has played a central role in the understanding of the pathology, pathogenesis, transmission, diagnosis and epidemiology of these diseases and their human counterparts. This work has not only made a major contribution to containment of BSE, and to animal health issues, but has contributed to the protection of public health directly. At present, best estimates available suggest that BSE will die out from the national herd by 2001, but if a causal link between BSE and nvCJD is established, any increase in incidence of nvCJD in the population would most probably occur after the BSE epidemic, because of the long incubation period.
9. This paper cannot do justice to all the knowledge already generated by work in relation to TSEs in animals, but it does refer to priorities in the animal field, which appear to be of direct relevance to human health. A major component of this paper is a statement about the R&D requirement, at the time of writing. The strategy has to evolve if it is to respond to new developments and an expanding information base. It will be updated as required.
10. The scope of the strategy covers issues pertaining to human health. It does not cover, except insofar as it has an impact on public health issues, the research programme undertaken by MAFF and the research councils related solely to animal health. In any such document, certain aspects are more urgent than others and the paper indicates priorities from the perspective of protecting public health. It is essential to emphasize that the R&D issues of importance in TSEs, require long term study, due to the very nature of the disease under investigation. Conventional funding approaches providing “short term” support for 2 to 3 years are of limited value and many studies will require longer term support. Furthermore, applied research cannot be divorced from basic studies into molecular and biological aspects of TSEs, and further developments in diagnosis and therapy are totally dependent on continuing support of research into the fundamental aspects of this disease.

## **Funding bodies**

11. The main R&D funders in this area are MAFF, BBSRC, MRC and the Health Departments, but a number of other government departments and non-governmental public bodies also have specific and focused R&D responsibilities in this area, e.g. the Health and Safety Executive (HSE).

12. The contribution from charitable bodies into TSE research is limited and given the more focused remit, not on the scale of cancer or heart disease. However, the Wellcome Trust has made and continues to make a substantial and important contribution.

### **Work with European and other partners**

13. The European Union (EU) has considerable powers, with respect to public health across Europe, and a wide ranging R&D remit. It has taken a number of steps to give priority to further work on spongiform encephalopathies.
14. The Science, Research and Development, Life Sciences and Technologies Directorate (DGXII), has addressed prion research, at the European level, as one of the priorities within the Biomedicine and Health programme (BIOMED) (1990-1994) and the Biotechnology programme (BIOTECH) (1990-1994). Reinforcement of prion diseases research has continued within the BIOMED2 programme (1994-1998).
15. A Working Group, established by Franz Fischler and chaired by Professor Charles Weissmann, under the auspices of the Agriculture and Rural Development Directorate (DGVI), was convened, with the responsibility of examining Europe wide research on BSE and proposing precise scientific priorities for Community research projects. The recommendations from this Group have very recently been published and the UK will consider this report as soon as possible.
16. The UK looks forward to working with European partners in any intensification of R&D in this area.
17. The WHO has an international remit in this area and has taken steps to consult internationally on pathology, surveillance and research. A formal report of the consultation meeting has been published and has been taken into account in drafting this strategy.
18. This document does not pursue the possible role of industry. Although commercial interest, in what is currently a rare disorder, is likely to be limited, there are extensive programmes of research into neurodegenerative diseases, such as Alzheimer's and into the development of new diagnostic systems e.g. immunological methods. Collaboration in these fields should be encouraged in the funding of research.

### **Scientific advice**

19. In putting together this strategy document, the Director of Research and Development in the Department of Health has drawn on wide ranging advice. The sources of advice include: the meetings and publications of SEAC; a series of scientific meetings set up specially to examine the priority and feasibility of research in this area as a whole, and in relation to basic biological work and epidemiology; experts from all the R&D funding bodies. In addition MAFF reviewed their priorities in 1995 using a group of academic experts from relevant fields and the BBSRC's annual BSEP workshop provides a forum for discussion of the latest research results and assessment of progress. All these sources will continue to inform the strategy and when further advice is available from Europe and WHO this will need to be incorporated.

### **Major R&D directions in TSEs with respect to human health**

20. The question of immediate public concern is whether there is a link between BSE and the nvCJD. It is also essential, particularly if this link is established, that the understanding of the causes and pathophysiological processes giving rise to the human disease, is greatly improved, that we have better scientific knowledge of the routes and mechanisms of infection, and of the susceptibility and protective factors associated with CJD. This knowledge will speed the development of techniques for early diagnosis, improve measures taken already to protect public health and provide a better basis for future approaches to essential prevention work.
21. Essential questions can only be addressed by an R&D strategy which spans the whole spectrum from basic biological studies of molecular structure, through a variety of more applied studies to epidemiological work and risk assessment. As will become apparent from this strategy, these components are inter-dependent. The urgent requirement for better methods of detecting the infective agent requires that we know much more about it. Knowledge from several different fields and research approaches has to be properly integrated to address the important issues that are raised. Thus, definition of disease at the molecular and cellular level has to be complemented by clinical and epidemiological studies. By the same token, much of the infrastructure required is common to several areas of study. Any successful research strategy in this area requires therefore, both clinical and epidemiological research supported by biomedical investigation at the molecular, cellular and tissue level into the nature of the infective agent and its mode of action.
22. It is clear that progress now needs to be made in a large number of areas and these are outlined in the following sections.



## A. THE NATURE AND FUNDAMENTAL BIOLOGY OF TSEs

23. The nature of the agent responsible for this group of diseases is still not understood. Research into the biology of SEs, including the nature of the agent, is of fundamental significance and underpins any attempt to address the applied questions relevant to human diseases.
24. The “protein only” theory is currently the most favoured hypothesis. Prion protein (PrP) is a sialoglycoprotein, encoded for by the PrP gene, and highly conserved in animals. The normal function of PrP is unknown, despite its presence in different organs and tissues, including the brain. In the brain tissue of clinically affected TSE animals, an abnormal form of PrP (PrP<sup>Sc</sup>) is found, which is thought to be derived from the normal form.
25. The areas that are of major importance in relation to human health (and animal health) are:

### i) Nature of the infective agent

26. Two aspects of the nature of the infective agent have an immediate bearing on human disease. Firstly, is the “protein only” hypothesis correct; if not what are the other components of the infective agent? Secondly, what is the inter-relationship between the “prion” and the normal PrP gene? Answers to these questions are fundamental to inform further work on transmission and the development of diagnostic and therapeutic approaches.
27. Addressing these issues will require the development of *in vitro* systems to determine if replication and conversion of PrP can occur in a cell free environment and how information obtained from such systems can be applied to developing diagnostic tests. More detailed information on the tertiary structure of PrP/PrP<sup>Sc</sup> is needed, as this will be the basis on which physico-chemical interaction of the agent will be established and provide for molecular modelling of agents that might inhibit this process. Again advances in this area are likely to depend on efficient expression of PrP<sup>Sc</sup> as fragments in a variety of hosts including cell lines. These expression systems could be used more directly in diagnosis and screening of candidate compounds, e.g. lead compounds.

### ii) Strain variation

28. This issue is closely linked to the nature of the agent. If there is no nucleic acid in the infective agent, a mechanism for species variation has to be identified. The results of these studies will therefore be relevant in determining the nature of the infective agent and in relation to the phenotype of the human diseases associated with TSEs. It will thus have important implications for transmissibility and future epidemiological surveillance, as well as having an obvious bearing on the development of therapeutic agents. However, the basis for strain typing, which is determined by mouse bioassay, has not been established. Studies are needed to elucidate the biological mechanisms in order to fully interpret the significance of strains identified by mice.

### iii) Genetics of PrP and TSE

29. A greater understanding of the role and nature of the normal PrP gene and its products will enhance our knowledge of the basis of the pathological phenotype, e.g. is it linked to loss of normal PrP function? It is clear from initial studies that other genes may influence the phenotype of disease, and such influences need to be defined in detail, as this will have a bearing on the biology, pathogenesis, diagnosis, epidemiology and particularly the definition of the “at risk” population for future prevention strategies. It may also be of importance in producing new therapeutic approaches. This work is relevant to animal health as well as human health.



## **B. IMPORTANCE OF ANIMAL MODELS**

30. At present, progress in understanding TSEs and how they affect human and animal health, is dependent on the study of animal models (e.g. cattle, sheep, non human primates, wild type mice, transgenic mice) of the disease because:-
- currently the “gold standard” means of detecting TSEs is by bioassay, therefore the whole diagnostic/transmissibility field requires access to animal models;
  - animal models provide the only realistic means by which disease progression and modification can be examined in detail, whether attention is focused on the impact of TSE strain variation, host genetic background, identification of candidate disease modifying host genes, or the impact of novel therapeutics;
  - they provide the only means by which criteria for environmental/exposure safety limits can be established and the only means by which such limits may be monitored.
31. Work needs to be undertaken to develop novel methods for both the qualitative and quantitative detection of TSEs, but until they are developed, animal models will remain a mainstay of all R&D areas. No single animal model can address all the issues raised in this strategy, so a range of models needs to be available, and there is also a need for new models to permit specific research questions to be addressed more accurately.
32. Transgenic mouse models and mice with varying genetic backgrounds are the most promising system for studying aspects of diagnosis and transmission and where possible should be further developed and refined. Because they have well defined genetic backgrounds, they may provide the only economic model in which to examine the effect of host genetic influences on TSEs. Several further developments of these models can be anticipated:-
- quantitative alterations of wild-type mouse genes including knockout, homozygous and over expression;
  - chimeric mouse/human PrP gene;
  - human genes expressed at various levels;
  - mutant human PrP gene over expressed;
  - other transgenes such as PrP variants and ApoE variants;
  - bovine and ovine transgenic models may considerably improve animal studies of pathogenesis, tissue infectivity and elucidation of the species barrier.
33. Non transgenic mice and other species will continue to be studied. For interspecies differences in disease progression, and transmission within the single host, mice will probably continue to be the mainstay of investigation into the mechanism of transfer of TSEs from point of entry, e.g. the gastro-intestinal tract, to the CNS.

34. Whilst the transgenic mouse models provide relative convenience, both in terms of the ability to house large numbers of animals and shorter incubation periods, as compared to large animals, their relative susceptibility compared to the host of origin will need to be established for each transgene. In other words the validity of transgenic mice as models for both human and animal diseases will need to be established before results from experiments using them can be considered as applicable to the disease in the natural host. Animal transmission studies need to be used to help establish environmental and food safety limits and hence will have a direct bearing on prevention and risk appraisal.
35. The necessity for carrying out work using non-human primates has been carefully considered, given the cost and security significance of work with primates. The variation in pathological and clinical characteristics of spongiform encephalopathies in different species is well documented. There are considerable risks in relying entirely on the mouse model for experimentation and extrapolation to humans. Except for individual studies with specific aims e.g. CJD into calves, non-human primates can complement and enhance the knowledge that will be generated by using other animal models, but their contribution needs to be carefully defined. Some strain typing studies, some work on genetic susceptibilities, possibly the development of *in vivo* brain imaging, second passage in primates, and exploration of possible new genetic forms of the disease may be issues on which work in non-human primates may be required. Some of the work identified above, could be carried out given modest primate facilities. The need for more ambitious work, particularly if transmission and environmental/food exposure work is to be performed in primates, will need careful consideration, as much larger primate facilities, operational over long periods of time would be required. The European Union is also considering studies in primates and the UK and the EU programmes will be closely coordinated.
36. Overall, the inescapable conclusion is that there is an urgent need for a considerable expansion of appropriate animal containment facilities. Some of this expansion has already been put in hand. It must be stressed that the reliance on the mouse model “bioassay” for TSEs, makes much of the research very dependent on the availability of facilities. Furthermore, the number and species required, may be large if the experimental design and statistical analysis is to be robust and valid. In considering these issues, account must be taken of the stringent Home Office health, safety and animal welfare requirements.

## C. TRANSMISSIBILITY

### i) Links between BSE and CJD

37. The issue of greatest current public and scientific concern is the possible relationship between BSE and the nvCJD, which, as yet has not been elucidated. In order to determine the possible relationship and yield conclusive answers, a complex, multidisciplinary approach to research is required. Transmission studies aim to confirm transmissibility between species. But a further question of longer term consequence to human health is the related issue of BSE transmission to other species, e.g. sheep.
- strain typing studies using transgenic mice expressing human PrP and wild type mice are being put in hand to determine if nvCJD produces the same pattern of disease in the mice as BSE agent does. Unfortunately, while a positive result will strengthen the likelihood that BSE is causally linked to nvCJD, negative results will not confirm or reject the hypothesis. Recent results using Western blotting indicate that nvCJD is a distinct and new sub-type of prion disease. This research needs to be followed up to confirm that a number of new CJD strains are not involved and hence determine whether there is one or more routes of infection;
  - several scrapie strains have been identified, in contrast to BSE, where it appears that only one strain of agent is responsible for the epidemic. However, relatively few isolates of CJD have been typed by transmission to mice and characterization by lesion profile, and incubation period. This work requires expansion and before conclusions can be drawn transgenic mouse models will need to be validated;
  - strain typing studies to elucidate the relationship between CJD and spongiform encephalopathies in other animals, will be required.

### ii) Routes of transmission

38. We need further research on how are these diseases transmitted both *within* species, and *between* species. What the role of vertical transmission is, what part horizontal transmission plays in the BSE epidemic. We also need to establish the mechanisms for maternal transmission, if it occurs, the size and timing of infective dose, the levels of infectivity during the incubation period and the persistence of infective agent in various tissues.
39. Within species, most research has been carried out in relation to scrapie, with infectivity assayed in conventional mice and several major hypotheses have been explored. Contaminated ruminant feed is accepted as the likely main route of transmission of BSE within cattle, together with the recent suggestion of low level maternal transmission. Important areas of further work in relation to human health are:-
- the likelihood of the oral route of horizontal exposure for CJD, presupposing the possibility of infective bovine material entering the human food chain;
  - the potential for horizontal transmission to man by other routes, their likely source and efficiency, e.g. blood, gut and respiratory mucosa, ocular membranes and dermal scarification;
  - routes of transmission specific for iatrogenic cases of CJD;

- further work on the possible maternal mode of transmission in cattle and its potential to generate alternative routes of human exposure - using species in which TSEs occur naturally, natural and experimental exposure and the most sensitive biological assay system;
- the nature of the species barrier and the donor species effect;
- the infective dose, the level of infectivity during the incubation period (in man and animals which represent a potential source of infection), the influence of age at first exposure, and the persistence of the infective agent in tissues.

### **iii) How does the agent cause disease?**

40. We do not understand the progression of the disease in man - from the site of exposure to the onset of clinical signs. The progression of infectivity from scrapie into different sheep tissues has been demonstrated using mouse models and appears to be the same in natural sheep scrapie. Following infection there is a “zero phase”, during which no infectivity is detected anywhere in the sheep; infectivity then appears in the lymphoreticular system, particularly the spleen, and later, and in higher titres, in the central nervous system. The possible transmission via the peripheral nervous system to the brain has also been identified using mouse bioassay. Studies of BSE are in hand that may elucidate the pathways of infectivity in cattle.
41. It is not known how much of this knowledge may be extrapolated to man, and such knowledge could be vital for the development of diagnostic methods and treatments. A better understanding of these pathways of infectivity is needed in man in particular to determine:-
  - the roles of gut permeability and gut acidity on progression of infectivity, (assuming an oral route of exposure);
  - how infection crosses the gastrointestinal barrier into the submucosa and how the agent transfers from the submucosa to the brain;
  - the respective roles of the lymphoreticular system, the nervous system or other vehicles in the transport and replication of the infective agent; why the brain is so susceptible;
  - the possible role of the peripheral nerves particularly with respect to routes of exposure other than oral;
  - the possible role of co-infections in compromising early defences;
  - the role of the immune system. If involved, is the agent transferred by uptake into endothelial/dendritic cells or is it directly transferred by lymphocytes?
  - the nature of the spongiform changes in brain tissue, their distribution within the central nervous system, and the mechanisms which initiate changes at cellular level;
  - the nature of amyloid aggregation and toxicity;
  - if there is evidence for a reservoir of sub-clinical infection in man, and animals;

- genetic susceptibility: although cattle appear to be equally susceptible to BSE, the host genome is clearly of importance in, for instance, the phenotype of the disease in mice and in familial CJD. Identification of pathogenic mutations in the PrP gene in humans has enabled the identification of some cases of apparently inherited prion disease, which would not otherwise have been identified. In most human cases of sporadic and iatrogenic CJD there is an excess of homozygous genotypes at codon 129 suggesting that heterozygosity may confer a measure of resistance. A considerable amount of research has shown the very close interplay between the scrapie agent and the sheep genotype.

#### **iv) Infectivity of tissues**

42. Mouse bioassays of tissues from sheep with scrapie have helped to establish which tissues are potentially able to transmit the infection. Similarly, cattle with symptomatic BSE, infectivity has been detected in the central nervous tissue, brain and cervical spinal cord and the retina, and, in experimental situations only, the distal ileum. No infectivity has been found in muscle, milk, udder, placenta, liver, kidney, blood, bone marrow, spleen, lymph nodes, semen and a range of other tissues.
43. Infectivity has been found in kuru cases in brain, spinal cord, kidney, spleen and lymph node; and in sporadic CJD cases in brain, cerebro-spinal fluid, kidney, liver, lung and lymph node, and in iatrogenic cases in pituitary gland (although not by bioassay methods), dura mater and cornea. Tissue infectivity studies continue to be important:-
  - for a better understanding of routes of infection and for public health protection where animal tissues and fluids enter the food chain;
  - for situations where a TSE occurs in a species donating tissues or body fluids for use in surgery or biological products;
  - for dose response studies and new methods of detecting infectivity.
44. Until recently, assays of infectivity in tissues have been determined by inoculation into mice. However, recent results have shown that mice are relatively insensitive to BSE compared to calves. In consequence, studies have been started and further studies are needed to confirm levels of infectivity of tissues in host species.



## D. DIAGNOSIS

45. Efficient diagnostic techniques are vital to the assessment of disease mechanisms, to diagnosing the presence of the disease in a patient, monitoring treatment efficacy and to epidemiological surveillance. In the case of CJD and spongiform encephalopathies in animals, diagnostic tools are considerably under-developed, primarily because so little is known about the nature of the transmissible agent and the causal mechanisms of disease.
46. Currently, diagnosis can normally only be confirmed *post-mortem* and is dependent on examination of brain tissue. Neuropathological examination of brain material (frontal, temporal, parietal and occipital cortex; basal ganglia; thalamus; hypothalamus; cerebellum mid-brain; pons and medulla) involves microscopically screening for spongiform changes and PrP<sup>Sc</sup> plaque formation, neuronal loss and astrogliosis, as well as conventional histochemical techniques and immunocytochemistry for prion protein.
47. Furthermore, this same standard of examination has to be applied for confirmation of infection in transmission studies and in detecting and confirming disease in naturally infected animal hosts. Therefore, it is a high priority to develop qualitative and quantitative techniques of TSE detection in tissues, especially at non-neuronal sites. Quantification is of particular importance, if studies of TSE burden in tissues are to be performed. These studies, in different species, could provide information on which to model both disease progression and the extent of human exposure.
48. Qualitative and quantitative techniques may also hold some promise for early diagnosis, which is believed to be of importance if potential therapies are to be successful. However, currently diagnosis is difficult and unreliable *ante-mortem*, being effective only late, if at all, in the course of the disease and being largely dependent on clinical evaluation, neurophysiology (EEG), and where possible, brain biopsy with immunoblotting/cytochemistry.
49. Improvements in these fields may not only improve diagnostic reliability, but may ultimately lead to disinvestment in the costly and time consuming use of mice for bioassay of TSEs.
50. The R&D effort in this area needs to continue to be focused on avenues of enquiry which are likely to lead to methods of diagnosis for both animals and humans which are effective both during the pre-clinical and clinical stages of the disease and which are able to differentiate CJD in man from other neurodegenerative diseases. Considerable resources have already been invested in this area and those techniques which are considered candidates for continued investigation include:-
  - electro-physiological approaches, e.g. EEG, can be strengthened by developing criteria for interpretation and statistical analysis. Magnetic resonance imaging (MRI), although not promising in cattle and mice, is a priority for further development for human application. Some work with MRI has started in humans and, with enhanced spectroscopy, may prove to be useful, particularly as it could be validated at autopsy. A focus on particular sites for MRI, e.g. the basal ganglia, could be explored. This is an area where it will be vital that those with the imaging expertise, work closely with those who have extensive and up to date knowledge of the pathology of the disease. If visual techniques of diagnosis can be developed successfully, biopsy of other tissues may become practicable and useful. Enhanced imaging facilities are likely to be required;

- a number of *in vitro* diagnostic tests have been put forward, involving cerebro-spinal fluid (CSF), blood and urine. The validity, specificity and sensitivity of these remain to be investigated, although work on CSF is most advanced. For example, the test developed to detect a protein marker for CJD in the CSF of clinically affected patients. Others are at an early stage of development. Metabolite markers in scrapie and BSE have been identified and it is hoped that these will accelerate the development of diagnostic methods for sheep and cattle;
  - tissue culture systems and cell lines, including tissues from spleen, lymph nodes, and tonsils may emerge as other candidates for diagnostic development, particularly if cell transmission is to be attempted.
51. The development of diagnostic tests for animal TSEs has an immediate bearing on protecting human health.
52. The development of diagnostic techniques for use in man is an area where collaboration with industry might be sought. It is likely to be most beneficial when more of the essential work outlined above, is further advanced.

## **E. ISSUES OF SAFETY, PRIMARY PREVENTION AND RISK ANALYSIS**

53. Equally as important as the R&D, which aims to elucidate the relationship between BSE and nvCJD, determine routes of transmission, and develop diagnostic techniques, are issues of public health protection. All measures considered prudent to protect public health are now in place, but further R&D is urgently needed to provide a firmer scientific base for these measures, or to indicate changes that may be needed.

### **i) Risk analysis**

54. Risk characterization exercises can document and measure systematically the wide ranging uncertainties about the antecedents of most types of CJD, and elucidate and help prioritize the potential and actual risks to public health. This will give new insights into where to focus new or changed preventative action, and may indicate where further research is required to help reduce uncertainty.
55. Studies of relative risk, and of the relation between actual risk and perception of risk are clearly of key importance to help with communication, media handling and political and public understanding of the issues involved.
- modelling of the BSE epidemic, incorporating data on incubation period, demography of the cattle population, consumption of meat and bone meal in supplementary feed, bovine age, and the notified incidence of BSE has yielded important insights but needs further attention;
  - modelling possible scenarios for the future incidence of nvCJD should be undertaken, and will rely on robust models from the BSE epidemic. nvCJD modelling will require more data on incubation periods, the length of time from onset of early clinical symptoms to death, and likely routes and sources of exposure.

### **ii) Food safety**

56. The single most pressing issue for public health protection is food safety, and a large part of the R&D programme to date has been targeted at determining the safety of meat and meat products. Work on infective pathways and the programme of studies on tissue infectivity, described elsewhere in this paper, have been designed to establish the safety of food. This programme of work will be continued and expanded as the need arises and is an essential part of this strategy.

### **iii) Other priorities**

57. Other areas that require priority research include:-
- studies of the possible risk to public health from non-food animal products;
  - risk assessment of potential environmental contamination arising from the disposal of culled carcasses and specified bovine materials;
  - definition of, and compliance with, safe working practices and processes, for the protection of occupational groups that may be at risk: farm workers, abattoir workers, those in related processing industries, laboratory workers. Each of these groups may be open to different routes of exposure in addition to exposure routes of the public at large, e.g. exposure from airborne particles and dermal scarification;

- indirect studies of the general risks from aerosols and dusts in the industries;
- studies of patient and staff exposure via invasive medical procedures and medical products - blood, vaccines, injectables, implants, pharmaceuticals and medical devices;
- further studies on effective methods of inactivation and decontamination for use on neurosurgical instruments and in laboratory environments and other workplaces. Particular interest could be paid to the development of combination treatments. The agents involved in BSE, scrapie and CJD are highly resistant to inactivation and although studies have indicated practical methods of disinfection, they are not 100% effective.

## **F. TREATMENT AND CARE**

58. Development of therapeutics for CJD is likely to be dependant upon the range of biological work outlined elsewhere in this paper. Already, preliminary studies suggest that agents such as Congo Red, amphotericin B and pentosanpolysulphate may have beneficial effects in producing inactivation and/or on slowing the rate of disease progression. Whilst detailed examination of potential lead compounds is of major importance, the interdependence of R&D in TSE research is of crucial importance in this field.
59. It is obvious that a basic understanding of the nature of the prion will be important and the development of diagnostic tools and transmission models of the disease are equally important in the ability to study potential therapeutic agents. It is not premature to discuss with the pharmaceutical industry approaches for screening candidate compounds and establishing criteria for their initial examination and this communication would provide an excellent opportunity to exploit industrial/academic interaction.
60. It is equally important to mount health services research to determine effective and cost effective approaches to palliative care, and to meeting the emotional and psychological needs of families. This work would have significant relevance to the care of other patients with rare and distressing diseases.



## **G. SURVEILLANCE AND EPIDEMIOLOGY**

61. There is a systematic identification of CJD cases in the UK and a detailed database of cases extending back to 1970. Seventy per cent of cases are validated neuropathologically including immunocytochemistry, and brain and peripheral tissues including blood are systematically checked and archived for further studies, in a tissue bank in the CJD Surveillance Unit at Edinburgh. This gives rise to a number of scientific opportunities.
62. High priority has already been given to continuing and strengthening this work, and collaboration with similar surveillance initiatives across Europe has good potential to increase the number of cases available for study, of sporadic and other types of CJD, enhance epidemiological work, and yield early warning of nvCJD identification. Liaison with other countries beyond Europe, e.g. Canada, Australia, Israel, is developing and is of great importance, particularly for comparison with areas where BSE or scrapie are rarely found. Working with the WHO to establish more extensive surveillance is also a priority. The R&D effort could be substantially enhanced if there were agreed procedures for autopsy and for the preservation of tissues after death.
63. Although epidemiological studies on BSE are well advanced in the UK, such studies need to be continued and expanded. Epidemiological studies in animals are essential to the assessment of any current and future risk to man from this group of diseases.
64. Human epidemiological studies are essential to help identify factors that might be involved in causal mechanisms. Approaches which have been identified as being potentially useful include:-
  - establishment of paediatric surveillance;
  - more intensive examination of elderly populations with atypical dementias and other neurodegenerative disorders;
  - the expanded use of robust investigative procedures normally used in examining outbreaks of communicable diseases;
  - continued investigation of apparent clusters to throw up, confirm or reject hypotheses, and the follow up of any new hypotheses about routes of exposure;
  - case control studies of normal diet (which will require prior validation studies and an audit of products likely to carry infection); examination of the possibility of contact with contaminated feed;
  - studies of possible exposure at work to identify and complement studies of occupational safety covered in section E.

### **Priorities for human health R&D in relation to TSEs**

65. The sections above all identify major R&D needs in relation to TSEs and human health. Within these boundaries the questions of immediate relevance and high priority are:-
- the nature of the relationship of new variant CJD and BSE, including current epidemiology and surveillance;
  - the transmissibility of BSE including aspects quantifying potential direct and indirect risk to man;
  - development of new diagnostic methods;
  - the nature of the agents and pathogenesis;
  - development and assessment of potential therapeutic agents.
66. Each of these themes overlap and cross the boundaries of the areas identified in the previous sections. In order for these themes to be investigated in the most cost effective manner, careful coordination between funding bodies will be required. In addition, it will be essential to share infrastructure and to foster a collaborative ethos to ensure that a focus is kept on work leading to a better understanding of the human health issues related to TSEs.

### **Workforce capacity**

67. In the UK there are several internationally respected research groups in this field - the CJD Surveillance Unit at Edinburgh, several UK departments of neuropathology and neurology; St Mary's Hospital Medical School; the Institute of Animal Health (Compton and the Neuropathogenesis Unit at Edinburgh) and the Veterinary Laboratories Agency (VLA). Although collaboration has been vigorously promoted, given the extent of the requirement for R&D, scientific, veterinary and medical expertise in the United Kingdom in the field of TSE research is concentrated in a small number of "centres of excellence". It is of paramount importance that these are put on a firm footing and that, in the interests of an expanding but cohesive research strategy, other researchers should continue to be encouraged to collaborate with these centres. This may be the most efficient and cost effective way of ensuring that the skill and knowledge base is gradually extended, in keeping with an evolving human health problem.
68. Further consideration must be given to training future scientists in this field. Two major difficulties to this can be identified. Firstly, the precise scale of the human health problem we are likely to encounter in the next 5-10 years is unknown. Secondly, the very nature of research in this field is more long term than in other areas of biomedical research. In evolving a strategy for TSE research this has to remain an important issue for the medium term to ensure that a cadre of scientists (human and veterinary, basic and applied) is established for the future.
69. A major strategic objective is to identify skills and, where relevant, foster collaborations, both in the UK and with research groups in France, Switzerland, Germany, Japan and USA. The

UK has particular strengths in transmission studies, genetics, imaging, neuropathology, structural studies etc. There is a clear need to extend the range of disciplines in TSE research as the R&D requirement can only be delivered if a multidisciplinary approach is encouraged. One of the dilemmas of study in this area, is that it may be seen by experienced researchers whose skills are most needed, as a short term issue and hence discourage participation. This strategy needs a long term commitment, and ways will need to be found of providing security to competent and committed researchers attracted to the area.

### **Scientific constraints and opportunities of the field**

70. There has undoubtedly been a considerable advance in knowledge of this field in the past few years. It must however be recognised that scientific advance must proceed steadily and much work will not yield answers in the short term. The nature of some of the experiments required to elucidate the most pertinent questions of transmission and pathogenesis is long term, e.g. prolonged incubation periods are required in current animal models. There are some inherently difficult questions which can only be resolved by the development of new animal models, or new methodologies and standardisation. There is likely to be a need to set up a mechanism to ensure the supply of reagents for those involved in research programmes.
71. Much of the work that is needed as part of this strategy has wider importance, particularly in relation to diseases that may be prion related. It is likely that much that is learned will have significance for neurodegenerative diseases in old age, and neuropathological disorders in younger people. Developing methods and exploring new uses of imaging, and the development of new animal models will inevitably provide a good basis for work in other fields. The basic biological knowledge generated, will add considerably to the scientific information base on protein structure and molecular genetics.
72. In order to ensure comparability and repeatability of research, banks of reagents (e.g. inocula and antibodies) need to be available to all researchers. They need to be developed by a co-ordinated approach by funders and major research groups.

### **Implementing the strategy**

73. To help develop and move this strategy forward the DH Director of R&D has appointed two advisory groups - the DH TSE R&D Funders Coordination Group and the joint DH/MRC TSE Research Advisory Group. The complete terms of reference and current membership of both these Groups are given in Annex 1.
74. The DH TSE R&D Funders Coordination Group has a remit to agree which body is appropriate to take forward each of the significant elements of the strategy, and to ensure complementarity of effort. The DH/MRC TSE Research Advisory Group has a remit to advise the DH Director of R&D and the MRC on a scientific strategy and priorities for basic and applied research on the human health aspects of SEs.
75. By June 1996, all funders had already given new priority to R&D in this area, and were beginning to move forward on the urgent and priority areas within their own forward plans which clearly form part of the coordinated strategy.

76. The current work and the future plans of the main funders of R&D in this area are documented below and over the course of the coming months, funders will be continuing to move forward their commissioning processes to put new research in hand. The strategy will be updated to take this into account as new research requirements are identified.

### **i) Medical Research Council**

77. MRC's principal investment in the field has been through core support for the BBSRC/MRC Neuropathogenesis Unit (NPU) and a collaborative project between the NPU and the CJD Surveillance Unit (CSU) on CJD strain typing. MRC has also supported neuropathology research at CSU (see Annex 3). The range of technological approaches that can be brought to bear on the difficult research questions is increasing. MRC supported groups have strengths in a range of relevant disciplines and approaches, such as human and mouse genetics, molecular and cell biology, the neurosciences, *in vivo* imaging, epidemiology and medical statistics. With its health mission, the Council also brings to the TSEs field the distinctive ability to manage research at the interfaces between basic, clinical and public health research.
78. New MRC initiatives, as a result the joint MRC/DH call for research proposals into TSEs, will be aimed at stimulating research in the following priority areas:-
- the biological and epidemiological relationship between nvCJD and BSE, and between CJD and atypical dementias;
  - the analysis, perception and communication of risk in relation to CJD;
  - early disease progression and diagnosis in life - including a distinctive focus on appropriate primate models and cutting-edge imaging technologies;
  - integrated molecular, epidemiological and clinical approaches to understanding the cause(s) of sporadic CJD;
  - rational approaches to developing therapy.
79. More innovative proposals will also be considered in the following areas where they do not duplicate strengths within the existing programmes of the BBSRC and MAFF:-
- molecular, genetic, cellular and functional approaches to elucidating mechanisms of TSE transmission, PrP replication, pathogenesis and clinical progression;
  - biological function of normal PrP;
  - molecular structure of the prion proteins.

### **ii) Ministry of Agriculture, Fisheries and Food**

80. Pathologists at the Veterinary Laboratories Agency (VLA) made the original diagnosis of BSE in 1986 and scientists there carried out the original epidemiological research to determine the cause of the disease. Since then, a large programme of work carried out by the VLA, as well as the Institute for Animal Health (IAH) and other research contractors, has played a central role in the understanding of the pathology, pathogenesis, transmission and diagnosis of BSE as well as its epidemiology.

81. The current MAFF research programme on BSE is divided into four main categories: diagnosis of BSE, and where appropriate, other TSEs; pathogenesis (and the identification of the etiological agent); transmission and epidemiology. These, however, are not rigid classifications and there is considerable overlap between them since the research in one area can have a bearing on that in another (see Annex 2 for further detail).
82. The MAFF programme of research on TSEs is kept under close review, and if necessary, amended in the light of the results of research and the recommendations of other expert groups appointed by international bodies e.g. EC, WHO, to ensure that it meets policy needs and delivers high quality research. In 1995 it was subject to review by independent experts. Future priority include:-
  - epidemiological studies, e.g. investigation of whether BSE occurs naturally in sheep, whether maternal transmission of BSE occurs and whether there is a variation of susceptibility in the national herd;
  - diagnostics, e.g. validation of diagnostic tests, the development of *ante-mortem* tests and novel approaches to diagnosis;
  - transmission studies, e.g. determination of whether BSE in sheep could be maintained by natural transmission, development of transgenic mice with multiple copies of the bovine PrP gene to provide a faster, more sensitive bioassay whilst not producing spontaneous disease;
  - pathogenesis studies, e.g. validation of strain typing in mice as a method of distinguishing TSEs, scrapie pathogenesis studies using sheep bioassay and development of transgenic models for pathogenesis studies;
  - other studies, e.g. authenticity studies on food for the detection of adulteration with specified offal and development of a TSE reagents resource.

### iii) Biotechnology and Biological Sciences Research Council

83. BBSRC has long recognised the potential significance of the TSEs and supports high quality basic and strategic research aimed at understanding the biology and pathology of these diseases. The research is financed through core funding at the Institute for Animal Health and the Biology of Spongiform Encephalopathies programme (BSEP) which was launched in 1990 in response to growing concern about the extent of the BSE epidemic. All this has helped to provide a national research base on which to take forward the priority research identified in this strategy.
84. Present research priorities, described below (see Annex 3 for further detail), resulted from those areas in which BBSRC had significant existing strengths. These are fundamental studies into the nature of the infectious agent which address questions relevant to human health including the possible relationship between BSE and nvCJD. There are studies on the structure and function of both the normal and abnormal forms of the prion protein in addition to projects investigating the possibility of nucleic acid involvement. Research into the development of reagents which are able to distinguish the abnormal form of PrP offers the potential to develop diagnostic tests. Ongoing strain typing studies are crucial to increasing our understanding of the relationships between the different diseases, transmissibility and the nature of the species barrier.

85. BBSRC sponsored research is in progress which aims to identify cell types involved in the uptake, replication and spread of infection in the lymphoreticular system and other peripheral tissues in the CNS. In addition, there are investigations to elucidate the normal function of PrP in the immune system, all of which have implications for the development of diagnostics. Studies on the genetic influences in disease susceptibility and pathogenesis in scrapie have been in progress for many years at the Institute of Animal Health. These have led to the identification of mutations in the PrP gene. The development of the transgenic, humanised mouse has been funded under the BSE programme at the Prion Diseases Group at St Mary's Hospital. These mice are now being used in studies of the BSE/CJD relationship. PrP null mice have been developed under the BSE programme funding and are being used for electrophysiological studies in order to investigate abnormal functions.
86. It is planned that additional resources will be used to expand the above areas of research to complement research funded by other sponsors as part of the national strategy.

#### **iv) Health Departments of England, Scotland, Wales and Northern Ireland**

87. The Department of Health and the Scottish Office Department of Health, jointly fund the National CJD Surveillance Unit at Edinburgh. The unit which was established in 1990, monitors the incidence of CJD and investigates the epidemiology of the disease. DH also funds the associated neuropathological work, and a programme of strain characterization to help investigate evidence for the link between BSE in cattle and CJD in humans. There is also linked genetic work and work on inactivation.
88. More recently DH has funded a major expansion of animal containment facilities at St Mary's Hospital Medical School, London, and the Institute for Animal Health (NPU and Compton). Significant new studies on transmission and strain typing are in the process of being commissioned from Dr Moira Bruce IAH and Professor John Collinge at St Mary's.
89. It is for DH to fund research at the more applied end of the basic-applied spectrum, while recognizing that much of the infrastructure and many of the approaches to important research questions are heavily inter-related. It is likely that work funded by DH will fall into the following broad areas:-
  - strain typing and related studies which elucidate the likely link between CJD in humans, and BSE;
  - studies which explore routes of transmission and exposure, identify risk factors, and predispositions for disease, or increase knowledge about protective factors and barriers to transmission;
  - epidemiological studies involving modelling CJD, improving surveillance, or following up hypotheses about causal mechanisms;
  - testing of advanced and promising diagnostic approaches for use in man; trials of therapies at an advanced stage of development; health services research;
  - public and professional perceptions of risk to health; approaches to risk assessment;
  - public health issues not falling to others;

## **v) The Health and Safety Executive**

90. The main priorities of the HSE, in conjunction with other agencies, are:-

- additional studies on methods for inactivation of TSE agents;
- occupational risks associated with the slaughtering and disposal of potentially infected animals, with an emphasis on the risks associated with airborne dispersal and droplet size (aerosols, dusts and liquid splash);
- incidence of zoonotic infections in abattoir workers and renderers as an indicator of possible exposure to BSE agent.

## **vi) The Wellcome Trust**

91. An internationally recognized programme centred on the molecular genetics of the human prion diseases, including a number of genetically determined “relatives” of CJD, is carried out at St Mary’s Hospital Medical School. The programme was established in 1990 and, in part, built on earlier MRC funded work.
92. The Wellcome Trust recently announced further support for research on CJD and BSE by means of a Wellcome Trust Principal Research fellowship for Professor John Collinge. The Wellcome Trust supports the Wellcome Centre for Research on the Epidemiology of Infectious Disease in the Department of Zoology in Oxford. This Group has recently published work on the epidemiology of the BSE epidemic in cattle.

## **Approach to commissioning**

93. Experience has shown that to ensure research is put in place to meet the needs of the strategy, funders may have to work in proactive commissioning mode specifying work in some detail. Each funding body has procedures which differ in detail but need to be rigorous, transparent and rapid. It is important that the procedures that funding bodies use are known and understood by the research communities, both in responsive and commissioning mode. Industrial collaborations, as well as university teams will be needed for parts of the strategy.



## **GLOSSARY OF ABBREVIATIONS AND SCIENTIFIC TERMS**

**Agent:** the infectious particle thought to be responsible for the spongiform encephalopathies

**Amyloid:** a fibrillar protein found in various pathological states

**Atypical dementias:** progressive loss of mental abilities

**BBSRC:** Biotechnology and Biological Sciences Research Council

**Bioassay:** estimation of the activity of a substance by comparing its effects on living organisms with effects of a preparation of known strength

**BSE:** bovine spongiform encephalopathy

**CJD:** Creutzfeldt-Jacob disease, a human spongiform encephalopathy

**CNS:** central nervous system

**CSF:** cerebro-spinal fluid that bathes the brain and spinal cord

**DH:** Department of Health

**EEG:** electroencephalogram

**EU:** European Union

**Exposure:** The natural event which initiates infection in the host

**Iatrogenic transmission:** accidental transmission of the agent as a result of medical or veterinary procedures

**Infective dose:** the number/quantity of organisms/agents required to initiate infection

**IAH:** Institute for Animal Health

**MRI:** magnetic resonance imaging

**MAFF:** Ministry of Agriculture, Fisheries and Food

**Maternal transmission:** transmission of the agent from dam to offspring

**MRC:** Medical Research Council

**NPU:** Neuropathogenesis Unit of the Institute for Animal Health

**Neuropathology:** the study and causes of and the changes produced in nervous tissue by disease

**nvCJD:** new variant CJD refers to those cases so far identified, with clinical onset of disease in 1994 and 1995, with previously unreported neuropathological changes

**Occupational exposure:** the initiation of a human infection in the course of the patient's occupation

**Pathogenesis:** the study of the disease causing process by an agent in relation to its host

**Phenotype:** characteristics manifested by an organism

**Post/ante-mortem:** after/before death

**PrP/prion protein:** The normal form is a host-encoded protein that becomes modified and partially protease resistant in infected tissue and accumulates around CNS lesions in transmissible spongiform encephalopathies

**R&D:** Research and development

**SBO:** specified bovine offal comprising brain, spinal cord, thymus, tonsil, spleen and intestine from cattle over 6 months old and thymus and intestine from cattle of any age

**Scrapie:** a spongiform encephalopathy of sheep

**SEs:** spongiform encephalopathies. Disorders affecting the brain in which small vacuoles are apparent under the microscope

**SEAC:** Spongiform Encephalopathies Advisory Committee

**Strain:** distinct isolates of an agent, distinguished by their different incubation periods and patterns of neuropathology when passaged in mice

**Transgenic:** a technique in which all or parts of genes from one animal are inserted experimentally into the genes of the embryos of another

**Transmissible:** agents or diseases that can be naturally or experimentally transmitted to the host species or other species

**TSE:** transmissible spongiform encephalopathy. Always fatal and thought to be caused by an unconventional infectious agent with a long incubation period

**Vertical transmission:** transmission of the agent by means other than horizontal or iatrogenic

**VLA:** Veterinary Laboratories Agency

**WHO:** World Health Organization

**Zoonotic infection:** human infection sustained through contact with a contaminated animal or animal part

## **LIST OF ANNEXES**

- 1. Terms of reference and membership of the DH TSE R&D Funders Coordination Group and the joint DH/MRC TSE Research Advisory Group**
- 2. MAFF current research programme**
- 3. Research Councils current research programme (BBSRC and MRC)**



## **TERMS OF REFERENCE AND MEMBERSHIP OF ADVISORY BODIES**

## **ANNEX 1**

### **1. DH TSE R&D FUNDERS COORDINATION GROUP**

#### **Terms of Reference**

The aims of the group are to ensure that the programmes of R&D funded in this field address priority issues of national interest and constitute a coherent strategy when considered as a whole. To achieve this aim the Group will:

- share information on the strategic direction of current programmes of R&D and on priorities and plans for future programmes, to produce a coherent R&D strategy.
- ensure as far as possible that there are no significant gaps in programmes and that undesirable overlaps are avoided.
- agree which body is most appropriate to take forward significant priorities, and remit them to the appropriate body.
- share information on selection processes and agree standards for quality control and handling results.
- provide a forum for discussion of joint work, and joint funding of programmes, projects, facilities and expertise.
- share information about funding and funding plans.
- encourage collaboration between research teams in this area, and the sharing of scientific knowledge.
- share information about funding and programmes of research with relevant European bodies.

## **1. DH TSE R&D FUNDERS COORDINATION GROUP**

### **Membership List**

#### **Chairman**

Professor John Swales  
Director of Research and Development  
Department of Health

#### **Secretariat**

Dr Phillipa Towlson  
Research and Development Division  
Department of Health

#### **Members**

Dr Jeremy Metters  
Deputy Chief Medical Officer  
Department of Health

Dr Eileen Rubery  
Health Aspects of the Environment and Food  
Division  
Department of Health

Dr Ailsa Wight  
Health Aspects of the Environment and Food  
Division  
Department of Health

Mrs Jenny Griffin  
Research and Development Division  
Department of Health

Sir Robert May  
Chief Scientific Advisor  
Office of Science and Technology

Sir John Cadogan  
Director General of Research Councils  
Office of Science and Technology

Dr Margaret Bryant  
Research Management Group  
Medical Research Council

Dr Kate Brown  
Chief Scientists Group  
MAFF

Dr Danny Matthews  
MAFF

Professor Ray Baker  
Chief Executive  
BBSRC

Ms Meg Wilson - Alternative  
BBSRC

Dr David Gordon  
Programme Director  
Wellcome Trust

Dr Pat Chisholm - Alternative  
Wellcome Trust

Dr Pat Madden  
Scottish Office Department of Health

Professor Richard Edwards  
Office of Research and Development  
Welsh Office

Dr Liz McWhirter  
Research Management Branch  
Northern Ireland Office

Dr Mark Bale  
Health and Safety Executive

## **2. DH/MRC TSE RESEARCH ADVISORY GROUP**

### **Terms of reference**

- a) To advise the DH Director of R&D and the Medical Research Council on a scientific strategy and priorities for basic and applied research on the human aspects of spongiform encephalopathies, covering biomedical, epidemiological and health service research in relation to:
- antecedents of CJD and factors associated with it (including genetic disposition); the links between human spongiform encephalopathies and animal manifestations; transmission studies.
  - epidemiology and modelling.
  - infectivity of human tissues and the human health aspects of relevant animal regulations and of environmental issues.
  - approaches to assessing risk to human health in this area; public and professional perceptions of risk to health.
  - other research matters considered likely to have a significant bearing on the public health.
- b) To advise MAFF, BBSRC and other funders, should there be human health implications for their programmes.
- c) To advise on the resources needed to move the priorities forward in relation to:
- facilities
  - expertise
  - methodological development
- d) To take into account:
- scientific opportunities
  - public health concerns, including the recommendations of SEAC
  - constraints particular to the field
  - strategies and programmes of all major funders.
- e) To assist DH and MRC in developing mechanisms for stimulating new high quality proposals.
- f) To assist in the selection of outlines for working up into full proposals, as the need arises.

## 2. DH/MRC TSE RESEARCH ADVISORY GROUP

### Membership List

#### Chairman:

Professor Lesek Borysiewicz  
University of Wales  
College of Medicine

#### Invited Guest:

Professor John Swales  
Director of Research and Development  
Department of Health

#### Members:

Dr Trevor Robbins  
Department of Experimental Psychology  
University of Cambridge

Professor Ingrid Allen  
Department of Neuropathology  
Queen's University Belfast

Professor Eugene Paykel  
Department of Psychiatry  
University of Cambridge

Professor Brian Anderton  
Department of Neuroscience  
Institute of Psychiatry

Professor Mark Gardiner  
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## MAFF RESEARCH PRIORITIES

## ANNEX 2

The main contractors are the VLA and the IAH. These institutes have considerable experience in the animal TSEs; the research programmes on scrapie at IAH has been running for decades. Other contractors have also been supported where appropriate, such as the Institute of Zoology, the Moredun Institute and the University of Birmingham. It is hoped that expansion of the research programme will draw new scientists into the field through the development of new collaborations with the existing centres of research.

The current strategy for the MAFF research programme is set out below within four areas. The programme already includes some projects on sheep scrapie and it is expected that scrapie research will be expanded in parallel to that on BSE.

### Epidemiology of BSE

- identification of the risk factors and specific events which give rise to clinical disease in cattle;
- monitoring of the epidemic in order to:
  - identify means of transmission other than via food, if any, and to quantify the frequency of such occurrences should they occur in order to predict their effect on future incidence;
  - to assess the effectiveness of current statutory controls, and the need for further changes;
  - to predict future incidence of BSE and of TSEs in other non-human animal species in order to determine the association with BSE in cattle, if any, so as to permit an assessment of the potential long term implications for both animal and human health.
- to improve on current case definitions in bovines and other species in order to ensure detection of emerging disease and changes in epidemiology.

### Pathogenesis of BSE (and the identification of the etiological agent)

- determination of the mechanisms of entry to and spread of the infectious agent and the distribution of the agent within the body of infected cattle;
- identification, characterization and evaluation of pathological, histological, physiological and biochemical changes resulting from infection which could be of diagnostic significance, and lead to new diagnostic tests;
- identification and characterization of the etiological agent;
- identification of host factors that influence susceptibility to disease.

### Diagnosis of BSE and where appropriate other TSEs

- improvement on sensitivity and specificity of current *post-mortem* diagnostic procedures and the identification and evaluation of potential new *post-mortem* diagnostic tests;
- development of BSE specific tests applicable to the live animal (*ante-mortem*) both in the preclinical and clinical phases of infection, taking into account the need to restrict sampling of farm animals to easily accessible tissues.

### **Transmission of BSE**

- identification of those bovine tissues in subclinical/preclinical and clinically affected animals which contain detectable levels of infectivity using mouse and host species bioassays;
- identification of which species are susceptible to experimental infection with BSE;
- validation of the mouse bioassay for infectivity (to determine the extent of underestimation of infectivity titre caused by conducting bioassays across a species barrier);
- determination of whether vertical transmission is a significant route of transmission and to test the effectiveness of internationally agreed standards in the collection and storage of embryos in eliminating the risk of transmission of BSE by embryo transfer;
- testing the hypothesis that changes in the rendering industry permitted infectivity to pass through the rendering process in sufficient quantity to infect cattle;
- determination of what, if any, chemical or physical treatments will completely inactivate the agent of BSE, to measure the extent of the reduction in titre of partially effective treatments and to comparatively validate previous work with scrapie.

The MAFF TSE programme of research is kept under close review to ensure that it meets policy needs and delivers high quality research. In 1995 it was subject to review by independent experts. Future priorities include:

### **Epidemiology**

- investigation of whether BSE occurs naturally in sheep;
- methods of inactivation of infectivity;
- further studies to determine whether maternal transmission of BSE occurs and whether there is a variation of susceptibility in the national herd;
- studies to investigate whether susceptibility is related to age;
- strain typing of additional cases of both BSE and scrapie from the UK and other countries. This is essential if the epidemiological of BSE in the UK is to serve as a model for others;
- epidemiological of scrapie in the UK and elsewhere.

### **Diagnosis**

- validation of diagnostic tests and the development of an *ante-mortem* test;
- novel approaches to diagnosis - an Open Competition for proposals has recently been held in this area;
- extension of studies on diagnosis tests for BSE to scrapie;
- development of better, more specific antibodies to PrP<sup>Sc</sup>.

## **Transmission**

- investigation to determine whether BSE in sheep could be maintained by natural transmission if it occurs in a flock;
- development of transgenic mice with multiple copies of the bovine PrP gene to provide a faster, more sensitive bioassay whilst not producing spontaneous disease;
- use of embryo transfer to investigate the interaction of host genetics and scrapie/BSE development and transmission;
- investigation of whether parasites have any role in the transmission of TSEs.

## **Pathogenesis**

- validation of strain typing in mice as a method of distinguishing TSEs;
- scrapie pathogenesis studies using sheep bioassay;
- development of transgenic models for pathogenesis studies;
- genetic influences on disease susceptibility and pathogenesis;
- studies on the mechanism of transmission of scrapie in sheep;
- an attack rate study of scrapie in sheep;
- comparative assay of TSE in sheep and mice;
- cellular and molecular basis of peripheral and central nervous system pathogenesis;
- nature of the infectious agent;
- the molecular basis of strain variation.

## **Other**

- authenticity studies on food for the detection of adulteration with specified offals;
- development of a TSE reagents resource.



## **RESEARCH COUNCILS CURRENT RESEARCH PROGRAMMES (BBSRC and MRC) ANNEX 3**

### **BIOTECHNOLOGY AND BIOLOGICAL SCIENCES RESEARCH COUNCIL**

#### ***IAH - Competitive Rolling Grant***

#### **The nature and fundamental biology of TSEs**

- nature of the agent - protein only hypothesis, development of *in vitro* systems;
- structure, folding and stability of PrP forms;
- molecular pathogenesis of disease: the biochemistry of PrP<sup>C</sup>, PrP<sup>Sc</sup>, *in vivo* and *in vitro*;
- PrP ligands, their interactions and potential therapeutic value;
- strain variation;
- pathogenesis - central and peripheral nervous system;
- studies on the species barrier;

#### **Importance of animal models**

- transgenic mice models;
- sheep genetics - survival of highly susceptible sheep in the NPU Cheviot flock, expression of patterns in sheep, maternal transmission, genetics of sheep from scrapie free countries;
- mouse genetics;
- PrP null mice;
- gene targeting;
- strain variation and strain targeting;

#### **Transmissibility**

- links between BSE and CJD - strain typing studies on scrapie, BSE and nvCJD (this was started at NPU in the standard panel of mice using core funding);
- routes of transmission - the role of the immune system, pathogenesis;
- infectivity of tissues - mouse bioassays, tissue culture systems;

## **BSEPII**

### **The nature and fundamental biology of TSEs**

- protein structure and function;
- scrapie pathogenesis, peripheral and CNS;
- strain typing;
- further development of *in vitro* systems for PrP analysis;
- characterization of candidate nucleic acids;
- electrophysiological changes responses to scrapie infection - wild type and PrP null mice;

### **Importance of Animal Models**

- scrapie pathogenesis;
- sheep genetics;
- scrapie strain variation in transgenic mice;
- PrP null mice;
- neuron-PrP-glial responses in pathogenesis;
- further development of transgenic models for transmission studies and the nature of the species barrier. Projects funded by both competitive rolling grant and BSEP inevitably cover more than one research theme.

### **Awards to Universities**

University of Edinburgh  
Department of Pathology  
Neuronal pathology in CJD. An immunocytochemical study with quantitative macroscopic and microscopic analysis  
Dr J Ironside

36 months 01.08.95-01.08.98

University of Edinburgh  
Department of Physiology  
An analysis of the loss of synaptic function in the scrapie infected CA1 pyramidal neurones of mouse hippocampus  
Dr N MacLeod

24 months 01.09.95-01.09.97

University of Edinburgh  
 Department of Physiology  
 An investigation of neuronal properties, synaptic function and plasticity in the brains of PrP-null mice and other PrP-mutant mice  
 Dr N MacLeod

36 months 01.08.96-01.07.99

University of Edinburgh  
 Institute of Cell and Molecular Biology  
 Study of mice with gene-targeted alterations to the PrP gene  
 Dr D Melton

48 months 01.04.95-01.04.99

University of London  
 Biochemistry and Molecular Biology Department  
 Use of a transgenic model of human prion diseases for transmission studies  
 Professor J Collinge

36 months 24.11.95-24.11.98

***Awards to BBSRC supported Institutes***

Institute for Animal Health, Compton  
 Department of Molecular Biology  
 Scrapie strain-typing and PrP analysis in cell culture  
 Dr C Birkett

48 months 01.04.95-01.04.99

Institute for Animal Health, Compton  
 Immunopathology Unit  
 Phage antibodies recognizing PrP  
 Dr J Young

24 months 01.04.95-01.04.97

Institute for Animal Health, Edinburgh  
 Neuropathogenesis Unit  
 An investigation of scrapie pathogenesis in the spleen using immunodeficient transgenic and chimeric mouse models  
 Dr M Bruce

48 months 01.04.95-01.04.99

Institute for Animal Health, Edinburgh  
 Neuropathogenesis Unit  
 Determining the mechanism of neuronal degeneration and its relationship to PrP in scrapie pathogenesis  
 Dr J Fraser

36 months 01.07.95-01.07.98

Institute for Animal Health, Edinburgh and Compton  
 Neuropathogenesis Unit  
 Physical structure, folding and stability of PrP protein forms  
 Dr J Hope

36 months 01.07.95-01.07.98

Institute for Animal Health, Edinburgh  
Neuropathogenesis Unit  
Study of sheep PrP gene variants in transgenic mice  
Dr N Hunter  
48 months 01.04.95-01.04.99

Institute for Animal Health, Edinburgh  
Neuropathogenesis Unit  
Scrapie strain variation and targeting in transgenic mice with glycosylation deficient PrP  
Dr J Manson  
48 months 01.04.95-01.04.99

Institute for Animal Health, Edinburgh  
Neuropathogenesis Unit  
A study of genes with altered expression in PrP-null mice to identify the function of PrP  
Dr J Manson  
36 months 01.04.95-01.04.98

Institute for Animal Health, Edinburgh  
Neuropathogenesis Unit  
Nature of the scrapie agent. Characterization of candidate nucleic acids  
Dr R Somerville  
24 months 01.04.95-01.04.97

Institute for Animal Health, Edinburgh  
Neuropathogenesis Unit  
*In vitro* investigation of neuron-PrP-glia interactions in the pathogenesis of scrapie  
Dr A Williams  
36 months 01.04.95-01.04.98

The total funding for the projects listed above (awards to Universities and awards to BBSRC Supported Institutes) is £3,977,064, with a further £1.1m p.a. for core projects at IAH, (see below).

### ***BBSRC Core funded TSE projects to IAH***

#### **Compton**

- Structural and functional studies on the PrP protein;
- Molecular studies on scrapie and BSE prophylaxis;
- Development of *in vitro* cell systems for replication of the scrapie agent;
- Scrapie associated fibrils and polymeric PrP.

## **NPU**

- Role of PrP in transmissible spongiform encephalopathies using PrP null mice;
- Role of glia and inflammatory mediators in chronic neurodegenerative disease;
- Strain variation in scrapie and related agents;
- Peripheral pathogenesis and pathology of scrapie;
- Investigation of scrapie pathology in the central nervous system;
- Pathogenesis of scrapie in the central nervous system;
- Post transcriptional control of PrP mRNA expression;
- Role of PrP in the molecular pathology of scrapie;
- Scrapie disease in PrP deficient mice;
- transgenic mice with mutant PrP genes.

## **MEDICAL RESEARCH COUNCIL**

At present the MRC contributes 30% of the core funding Research Council income of the joint BBSRC/MRC Neuropathogenesis Unit in Edinburgh, a component of the BBSRC Institute for Animal Health (IAH) at Compton, Berkshire, amounting to approximately £600k per annum. In addition, in March 1994, the Council awarded a strategic supplement of £274k over 3 years for CJD related transmission studies, entitled "Strain characterization of the Creutzfeldt-Jacob disease agent by transmission to mice".

### ***Current MRC funded research projects in SEs***

Strategic project grant to Dr I Jones and Professor D Stewart (MRC Research Professor, Oxford University) entitled "Structure and function of the prion protein PrP<sup>C</sup>27-30" (1.10.96-30.09.99).

MRC link grant to Dr V Perry (Oxford) and Dr A Gearing (Neures Ltd) entitled "Inflammation in neurodegenerative disease: characterization of pathways in murine scrapie" (1.10.96-30.09.99).

A three year strategic project grant to Drs J Bell, J Ironside and R Will entitled "Prion protein in human spongiform encephalopathies" and a one year small grant to Dr R Colello entitled "The developmental expression of the prion protein gene in glial cells of the CNS" have both recently been completed.

The Council is working closely with all the major funders to promote research in the field of TSEs. In May 1996 the MRC and DH launched a joint call for research proposals in the field of TSEs and the proposals received have been shortlisted for further consideration by the joint MRC/DH TSEs Research Advisory Group.





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